ASSOCIATION OF KAPOSI'S SARCOMA AND PRIOR IMMUNOSUPPRESSIVE THERAPY

A 5-Year Material of Kaposi's Sarcoma in Norway

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A retrospective study of 53 cases with a histological diagnosis of Kaposi's sarcoma (KS) reported to The Cancer Registry of Norway during a five year period is presented. Four cases were excluded from the material because further information contradicted the diagnosis of KS. Of the remaining 49 cases, information of treatment received *before* the development of KS was obtained in 41 (83.7%). Six (14.6%) of the 41 patients developed KS during systemic treatment with corticosteroids, two of the 6 cases also used azathioprine. None of the patients had undergone renal transplantation. One additional patient had received radiotherapy for a malignant lymphoma prior to the development of KS. In a control group of 242 consecutive patients hospitalized because of basal cell carcinoma of the skin, none had used systemic corticosteroid or cytotoxic drugs. Case reports of the 7 patients with KS developing after immunopressive therapy are presented.

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KAPOSI'S SARCOMA (KS) is a rare malignant tumor in Scandinavia. The incidence of KS in Norway (population 4 million) is about 10 cases a year. The last 10 years, reports of 8 cases of KS have appeared in the literature, describing the development of KS during immunosuppressive therapy after renal transplantation.[11,12,13,14,15,21,24,25]

Several cases of KS that developed during therapy of malignant lymphomas or "autoimmune" disorders with immunosuppressive drugs have also been reported.[2,17,19,22] The present study discusses the possible role of prior immunosuppressive treatment in the development of KS, based on a 5-year material of KS in Norway.

MATERIALS AND METHODS

53 cases with a histological diagnosis of KS reported to The Cancer Registry of Norway during the 5-year period August 1970 to August 1975 were studied (registration of all new cases of cancer is compulsory in Norway). Four of the 53 cases were excluded because re-examination of the histological specimens and/or later biopsies contradicted the diagnosis of KS. Thirteen cases had been treated at The Norwegian Radium Hospital. Information concerning the other patients were obtained by a questionnaire to the doctors who had reported the cases to The Cancer Registry of Norway, asking whether the patient had received systemic treatment with corticosteroids or any cytotoxic drugs *prior* to the development of KS.

In order to evaluate the prevalence of systemic medication with corticosteroids and/or cytotoxic drugs in a comparable age group in Norway, the case records of all the 242 cases with basal cell carcinoma of the skin hospitalized during the period 1971–1974 in The Norwegian Radium Hospital were studied as a control group.

RESULTS

We obtained *some* information about earlier therapy in 41 (83.7%) of the 49 cases of KS. In many of the cases the information was rather scarce. It was possible that some of the patients had used corticosteroids or cytotoxic drugs before development of KS, even if this did not appear in their case records. In the control group the medication used at the time

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TABLE 1. Number of Patients Studied

	Number of patients
Total number of KS registered in Norway August 1970–August 1975	53
Excluded because of altered diagnosis	4
Reviewed (KS cases)	49
Treated at The Norwegian Radium Hospital	13
Data obtained from questionnaire	28
Evaluable regarding prior therapy (KS)	41
Control group (basal cell carcinoma)	242
Evaluable cases in the control group	242

of admission was always stated in the case records. The age and sex distribution of the KS cases and the control group are shown in Table 2.

Of the 41 evaluable cases of KS, we obtained positive information that 6 had used corticosteroids (prednisone or triamcinolone) *before* their KS became manifest. Two of the 6 cases had used the immunosuppressive (and cytotoxic) drug azathioprine (Imurel®) in addition to corticosteroids. One additional patient had received 4000 rad of radiotherapy to a modified mantle field for a malignant lymphoma 2 years before development of KS.

The 6 cases that had received immunosuppressive medication (corticosteroids with or without azathioprine) constituted 12.3% of the 49 histologically verified cases of KS registered in Norway during the 5-year period, and 14.6% of the 41 evaluable cases. If we include the patient who had received prior radiotherapy (with some assumed immunosuppressive effect), the corresponding proportions of immunosuppressed patients were 7/49 (14.3%) and 7/41 (17.1%), respectively.

Of the 242 control cases with basal cell carcinoma of the skin, *none* used corticosteroids (systemically) or cytotoxic drugs at the time of diagnosis. The difference between the number of patients using immunosuppressive drugs in the evaluable KS group (6 out of 41) and the control group (0 out of 242) was statistically significant ($p < 0.001$, Fisher exact probability test).

Further information of the 7 patients who had received immunosuppressive therapy before developing KS is presented in Table 3 and in the case reports below. The clinical and pathological subclassification are based on the criteria of Taylor *et al.*[26]

CASE REPORTS

Case 1–J.R., born 1904

From 1965 this patient was treated with prednisone, 10 mg/day (intermittently higher doses) because of severe bronchial asthma. In May 1970 he developed KS (clinically florid, histologically mixed type) with multiple blue tumors on the left foot and leg. There was some local response to radiotherapy, but his KS rapidly disseminated and he died December 19, 1972, from generalized KS. He used prednisone 10 mg/day or more until his death.

Case 2–O.J.H., born 1908

The patient underwent diagnostic laparotomy June 1, 1972, because of icterus which had developed April 1972. The hilar region of the liver was occupied of firm tumor masses, most probably an inoperable biliary duct carcinoma. A wedge biopsy from the liver showed biliary cirrhosis, a biopsy from a firm lymph node in the liver hilus showed only reactive changes. June 17, 1972, prednisone 10 mg × 2 was instituted because of progressive icterus. After a few weeks the dosage of prednisone was reduced to 10 mg/day. The liver function and the general condition improved. July 25, 1972, the patient noted blue tumors on the left foot and leg. The tumors increased rapidly in size and number. Biopsy showed KS (clinically nodular, histologically mixed type). The patient died September 15, 1972, of hepatic failure. The family did not allow an autopsy.

TABLE 2. Age and Sex Distribution

	Number of patients	Age			Males	Females
		Mean	Median	Range		
All KS cases	49	73.5	76	28–92	31 (63.3%)	18 (36.7%)
Evaluable KS patients	41	74.8	76	57–92	26 (63.4%)	15 (36.6%)
Prior immunosuppressive therapy, KS*	7	70.6	66	60–82	4 (57%)	3 (43%)
No prior immunosuppressive therapy	34	75.6	76	57–92	22 (64.7%)	12 (35.3%)
Control group (basal cell carcinoma)	242	66.3	67	25–92	136 (56.2%)	106 (43.8%)

* Including a patient who developed KS 23 months after radiotherapy with a modified mantle field because of malignant lymphoma.

TABLE 3. Characteristics of Patients Receiving Immunosuppressive Medication* Prior to Development of Kaposi's Sarcoma

Case	Indication for immunosuppressive medication	Type and dose of medication	Time from start of immunosuppressive medication to the first sign of Kaposi's sarcoma
1. (I.R.)	Bronchial asthma	Prednisone 10 mg/day	5 years
2. (O.J.H.)	Biliary cirrhosis	Prednisone 30–10 mg/day	1 month
3. (M.B.)	Rheumatoid arthritis	Triamcinolon 4–8 mg/day	8 years
4. (C.N.)	Polymyalgia rheumatica	Prednisone 20–7.5 mg/day	7 months
5. (R.F.)	Nephrotic syndroma	Prednisone 40–25 mg/day	4 months
		Azathioprine 150 mg/day	
6. (O.S.)	Pemphigoid	Prednisone 40–10 mg/day	7 months
		Azathioprine 150 mg/day	

* An additional patient developed KS 23 months after receiving 4000 rad of radiotherapy to a modified mantle field because of a malignant lymphoma.

Case 3–M.B., born 1908

The patient was treated with corticosteroids periodically from 1951 to 1965 because of rheumatoid arthritis. From 1965 she used triamcinolone (Kenacort® "Squibb"), 4–8 mg/day orally continually. In April 1973 multiple small blue-red tumors developed on the left lower arm and the left foot. Histological examination in September 1973 showed KS (histological specimen was not available for subclassification). Clinically the tumors were of nodular type. She continued medication with triamcinolone 4–8 mg/day. Her KS followed a rather "benign" course with slow-growing tumors developing on the feet and the lower arms. The tumors were treated with minor surgery and with radiotherapy with good local results. She was alive with no evident KS lesions in January 1978.

Case 4–C.N., born 1894

January 9, 1973, treatment with prednisone, 20 mg/day was instituted because of polymyalgia rheumatica. The symptoms were promptly relieved. In July 1973 the dosage of prednisone was reduced to 7.5 mg/day which she continued to use until June 1974. At the beginning of August 1973 she developed KS (clinically nodular, histologically mixed type) on the right foot, and in September 1974 on the left eyelid. The tumors responded well to radiotherapy, and there was no progression of her KS until the patient suddenly died (cause unknown) February 8, 1975. Autopsy was not permitted.

Case 5–R.F., born 1914

In July 1974 he developed a nephrotic syndroma of unknown etiology. He started treatment with diuretics and prednisone August 30, 1974. The initial dose of prednisone was 40 mg/day, after a few weeks it was reduced to 15 mg/day. Because of increasing albuminuria the prednisone dose was increased to 25 mg/day, and azathioprine (Imurel® "B.W. & Co.") 150 mg/day was instituted October 27, 1974. At the end of December 1974 he developed KS tumors (clinically florid, histologically monocellular type) on the right foot and calf, and in the following months his KS disseminated to the upper body, including the face. The lesions were treated with multiple fields of radiotherapy, with good local response. Medication with azathioprine and prednisone was discontinued in August and October 1975, respectively. His renal function has remained stable after this. December 1975 his KS progressed rapidly, but responded very well to radiotherapy and one course of chemotherapy with dacarbazine and doxorubicin. He was in complete remission when last seen January 1978.

Case 6–O.S., born 1897

Since 1970 the patient suffered from pemphigoid. Therapy with prednisone 40 mg daily and azathioprine 150 mg daily was initiated December 20, 1974. After a few weeks the dose of prednisone was reduced to 10 mg daily. His pemphigoid improved, but attempts at further reduction of the immunosuppressive medication resulted in aggravation of the disease. By the end of July 1975 he developed small KS lesions (clinically nodular, histologically mixed type) under his left foot. During August 1975 the tumors rapidly increased in size and number, and some tumors developed under the right foot. During September 1975, however, the growth of the lesions stopped spontaneously, despite continued and unaltered medication with azathioprine and prednisone. No

therapy of his KS was instituted, and all the lesions regressed completely or partially. He continued treatment with prednisone 10 mg/day and azathioprine 100–150 mg/day. His KS was still in nearly complete remission when last seen in September 1977.

Case 7–O.N., born 1891

In February 1971 she was treated with radiotherapy, 4000 rad, to a modified mantle field (excluding the axillae and lower mediastinum) because of an unclassifiable malignant lymphoma localized in the left side of the neck and in the left parotic gland (histologically the most probably diagnosis was Hodgkin's disease). She was well until October 1972, when she showed sign of progression of her lymphoma with enlargement of the spleen and anemia. Because of her old age and her own wishes, only blood transfusions were given. In January 1973 she developed KS (clinically nodular, histologically mixed type) on her right leg. She died in May 1973. An autopsy showed disseminated KS on both legs, in the spleen, in lymph nodes in both axillae and in the mediastinum. The spleen was also infiltrated by an unclassifiable malignant lymphoma which also affected a lymph node in the right axilla and the para-aortic lymph nodes. In addition the patient had a third malignant disease—a small undifferentiated gastric carcinoma without metastases.

DISCUSSION

The histogenesis of KS is still controversial. It has been proposed that the tumor arises from totipotent mesenchymal cells,[27] from undifferentiated vasoformative cells of the adventitia of blood vessels[10] or from the reticulo-endothelial system.[5] Patients treated with immunosuppressive drugs after renal transplantation seem to have a higher than expected risk of developing KS.[11,12,13,14,20,21,24,25] The present study also indicates an association between prior immunosuppressive therapy and development of KS, in patients who have not received a renal transplant.

Theoretically, there are several possible mechanisms for this apparent association. The immunosuppressive drugs may have an indirect carcinogenic effect by altering the immunological surveillance.[6] Immunological surveillance seems at least to be of importance in virus-induced tumors in animals.[1] The immunological status of KS patients may be impaired, at least in "the malignant form" of the disease.[18] The frequency of spontaneous regressions and the very good response to chemotherapy seen in patients with KS, may on the other hand indicate defense mechanisms against this tumor.[4] These defense mechanisms may be weakened by old age and/or immunosuppressive therapy. The regression of KS after reduction of the immunosuppressive therapy seen in some patients[14,20] may also be an indication of immunological defense mechanisms. However, one of our patients (O.S.) achieved a long-term "spontaneous" regression despite continued (and unchanged) medication with prednisone and azathioprine. Another patient had a rapid progression of his KS only 2–3 months after discontinuation of the immunosuppressive medication.

Warner and O'Loughlin[28] suggested that KS is the result of a chronic immunological reaction between antigenically altered or transformed lymphoid cells and normal lymphocytes. They proposed that in the course of this local graft versus host type activity, an angiogenesis factor is liberated and intense proliferation of mesenchymal and endothelial cells ensues. The cells responsive to the angiogenesis factor may then be transformed by an oncogenic virus.

This hypothesis may explain the association of KS and malignant lymphomas, and may be further extended to explain KS as a by-product of the chronic immunological reaction induced by an allograft or an autoimmune disorder. The associated immunosuppressive therapy may therefore possibly only reflect the need to treat the lymphoma, or suppress the rejection of the allograft or the autoimmune disease. Partial immunosuppression by drugs or irradiation may further aggravate the risk of malignant transformation in this setting, by impairing feedback loops controlling the immune response, as suggested by Schwartz.[23]

Some epidemiological, serological and electron micrograph studies suggest that a virus (cytomegali virus) may play a role in the development of KS.[7,8,9] Both the immunostimulation induced by an allograft or an autoimmune disease *and* the immunosuppressive therapy may enhance the oncogenic effect of viruses.[1,23,28]

It is possible that the immunosuppressive medication may have a direct carcinogenic effect. Cortiocosteroids inhibit immune processes, but they are not notably carcinogenic.[3] Azathioprine has a chromosome breaking effect *in vivo* in man.[16]

The interval between start of azathioprine

therapy and development of KS in the cases reported in the literature[11,12,13,14,17,20,21,24,25]—3 months to 4 years and in the two cases reported above (4 and 7 months, respectively)—is comparatively short, and shorter than one would expect for a direct carcinogenic effect in man.

In conclusion, there may be several possible mechanisms for the apparent association of KS and immunosuppressive therapy. The role of corticosteroids and azathioprine in the development of KS needs further studies. A purely random coincidence cannot be ruled out, but we find this possibility less likely. Obviously the risk of developing KS for the individual patient treated with immunosuppressive agents is very small. However, a connection between immunosuppressive therapy and development of a malignant disease may be easier to detect in a rare disease such as KS, than in the more prevalent tumor forms.

One should have the possible direct and indirect carcinogenic effect of immunosuppressive medication in mind, when such therapy is prescribed for nonmalignant diseases.

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